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PERIOD OF AGING AND MENOPAUSE

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- USSR -

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THE FUNCTION OF THE ADRENAL CORTEX IN WOMEN DURING THE PERIOD OF AGING AND MENOPAUSE

Following is the translation of an article by V. G. Baranov, I. Yu. Podol'skaya, and I. T. Rosovskaya entitled "Funktsiya Kory Nadpochechnikov u Zhenshchin v Period Stareniya i Klimaksa" (English version above) in Problemy Endokrinologii i Gormonoterapii (Problems of Endocrinology and Hormone Therapy), Vol. VI, No. 3, 1960, pages 95-103.

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In the process of aging and during the menopause, complex neurohormonal changes occur which determine a number of physiologic and pathologic peculiarities of this process (1, 2). However, in respect of age changes, especially as they occur in various parts of the neurohumoral system, and the dependence of these changes on each other, little has been written and that which has is unclear and contradictory. A clarification of these problems would be of great importance in gerontology and geriatrics.

In the present report we shall discuss the function

of the adrenal cortex in women at different periods of aging and the climacteric and shall attempt to give an analysis of the importance of the adrenal cortex in the formation and development of certain age changes of a pathologic nature.

A number of authors have shown that, in women and men, the urinary excretion of neutral 17-ketosteroids reaches a maximum in the third decade, after which it begins progressively to decline (3, 4, 5, 6, 7, 8).

But along with these investigators who have demonstrated during the aging process a reduction in the urinary excretion of 17-ketosteroids, Hamblen (9, 10) has observed during the period of the menopause an increase in the excretion of 17-ketosteroids, and Santo-Ruiz (cited by Wurthler, 8) has noted an increase in excretion of them during the period of the climacteric and a decrease following the climacteric.

Determinations of the 17-ketosteroid excretion in the urine, for studies of certain functions of the adrenal cortex, may be made with particular illustrativeness in women, in view of the fact that 17-ketosteroids in them are almost exclusively of adrenal origin, whereas in men, 10 to 30 percent of the 17-ketosteroids derive from steroids produced by the testes.

However, the total excretion of 17-ketosteroids in the urine principally characterizes one of the adrenal functions - the formation of C_{19} -steroids - and only a small part of the 17-ketosteroids are metabolites of C_{21} -steroids. In this connection, particular interest attaches to studies of urinary excretion of different fractions of 17-ketosteroids. According to the findings of Dorfman (11), in the 74-78 year age group there is a marked reduction in the urinary excretion of 11-desoxy-17-ketosteroids, along with a considerably less marked reduction in the excretion of 11-oxy-17-ketosteroids. Pincus and associates (12) also showed a negligible reduction in 11-oxy-17-ketosteroid excretion during the aging process. At the same time, 11-oxy-17-ketosteroids are metabolites primarily of cortisol and cortisone, and characterize the function of the adrenals with respect to the formation of this group of steroids. On the basis of urinalyses, Dorfman computed the formation of cortisone and hydrocortisone in the organism and concluded that there is little reduction in their formation in old women.

Albeaux-Fernet and associates (13) studied, in aging and old people, the changes in urinary excretion of 17-ketosteroids, 17-oxycorticosteroids, and total reduced corticoids, and noted, in the presence of a progressive decline in the

17-ketosteroid excretion, a less marked drop in 17-oxycorticosteroids and total reduced corticoids. However, the small number of works on the different age groups and the absence of statistical processing of the data make the conclusions presented by these authors of dubious value.

From these data it is evident that, although the question of changes in urinary excretion of 17-ketosteroids during aging and in old age has been well discussed in the literature, nonetheless the age dynamics of the blood and urine contents of 17-oxycorticosteroids has been studied only too little. In addition, with respect to 17-ketosteroids and 17-oxycorticosteroids, there are few convincing findings concerning their levels in the urine and blood in different periods of the climacteric and in menopausal neurosis.

In the present work we studied 94 women of three age groups (30-39, 40-49, and 50-59 years of age), with respect to plasma content of free 17-oxycorticosteroids, and the excretion in the urine of total and free 17-oxycorticosteroids and of neutral 17-ketosteroids. These findings were also compared in the groups of women aged 43-49 years, with persisting menstrual cycles and with menopause, with different durations of onset of menopause, and in the groups aged 40-54 years with and without menopause without menopausal neurosis.

Method

Free 17-oxycorticosteroids in the urine were determined by the method of Silber and Porter (14), as modified by Yudayev (15). Neutral 17-ketosteroids in the urine were determined by extraction with carbon tetrachloride, using the Zimmerman reaction (16). Blood for determinations of 17-oxycorticosteroids was taken from the vein in the fasting state, between nine and ten o'clock in the morning. Excretion of 17-oxycorticosteroids and 17-ketosteroids was determined in 24-hour urine samples.

Results

In studying the content of free 17-oxycorticosteroids in the plasma in women aged 30-39, 40-49, and 50-59 years, there was an observable increase in the average level in the 50-59 year age group (Table 1). However, with statistical

processing of the data for women of 30-39 and 40-49 years, we observed no reliable differences between them. The extreme limits of content of free 17-oxycorticosteroids in the plasma of women in the 40-49 and 50-59 year age group were within the limits for the younger women (30-39 years). We noticed no reliable differences in these age groups either with respect to the average excretion in the urine of total and free 17-oxycorticosteroids (see Table 1) or with respect to the extreme limits of their variation.

With respect to the average excretion in the urine of 17-ketosteroids in women of the three age groups (see Table 1), we detected a progressive decline in their excretion with increasing age, and the difference between these groups was statistically reliable.

In comparing the average plasma level of 17-corticosteroids, and the daily urinary excretion of 17-ketosteroids, along with the limits of their variation in women with menopause of less than two years' duration, of two to five years' duration, and in the age group with continued menses, we observed no reliable differences in any of these indices (Table 2).

In comparing the average level of these indices in the groups of women aged 40-54 years with menopause and with or without menopausal neurosis, we detected no significant differences in any of these indices (Table 3).

17-ketosteroids

Table 1

The content of free 17-oxycorticosteroids in plasma and of total and free 17-oxycorticosteroids and of 17-ketosteroids in the urine in women of different age groups

Age group	Average number of age (in years) studies	Average (mg in 24-hour urine)
A. 30-39 years	33	11
B. 40-49 years	45	33
C. 50-59 years	53	34

Groups A & B: $P < 0.05$
Groups A & C: $P < 0.05$
Groups B & C: $P < 0.05$

17-oxycorticosteroids

in urine				in plasma			
total		free		total		free	
average number of age studies	average (mg in 24-hour urine)	average number of age studies	average (mg in 24-hour urine)	average number of age studies	average (gamma in 100 ml blood)	average number of age studies	average (gamma in 100 ml blood)
33	8	33	8	34.4	18	34.4	14.2 ± 1.26
46	23	46	23	45.6	44	45.6	14.3 ± 0.69
52	19	52	19	53.1	32	53.1	17.5 ± 1.10

Groups A & B: $P > 0.05$
Groups A & C: $P > 0.05$
Groups B & C: $P > 0.05$

Groups A & B: $P > 0.05$
Groups A & C: $P > 0.05$
Groups B & C: $P > 0.05$

Groups A & B: $P > 0.05$
Groups A & C: $P < 0.05$
Groups B & C: $P < 0.05$

Table 2

Content of 17-ketosteroids in urine and of free 17-oxycorticosteroids in the plasma in women with menopause of varying duration

Group studied	17-ketosteroids			17-oxycorticosteroids		
	average age (in years)	number of studies	average (mg in 24-hour urine)	average age (in years)	number of studies	average (gamma in 100 ml blood)
A. Continued menstrual cycles (43-49 years)	45.0	14	7.3 ± 0.8	45.7	16	15.1 ± 1.26
B. Menopause less than 2 years' duration	48.4	11	6.8 ± 1.1	48.7	10	13.6 ± 1.70
C. Menopause of 2 to 5 years' duration	48.6	21	6.8 ± 0.5	49.6	21	15.5 ± 1.24
			Groups A & B: $P > 0.05$	Groups A & B: $P > 0.05$		
			Groups A & C: $P > 0.05$	Groups A & C: $P > 0.05$		
			Groups B & C: $P > 0.05$	Groups B & C: $P > 0.05$		

Discussion

As our studies have shown, in women in the period of aging (40-49, 50-59 years) there is a certain increase in the content of free 17-oxycorticosteroids in the plasma only in the 50-59 year age group, with no significant changes in the excretion of 17-oxycorticosteroids in the urine. These findings give us reason to state that, in the age periods studied by us, there are no significant changes in one of the most important functions of the adrenal glands - the production of 17-oxycorticosteroids.

We were also unable to demonstrate changes in these indices in connection with the onset of menopause in women, with duration of menopause of less than two years, and from two to five years, as compared with women of the same age still menstruating. As shown by the studies of O. N. Savchenko carried out in our own laboratory, in women in the first two years after the onset of menopause there is no decline in the average values for excreted estrogens such as occurs in the ensuing period. All of this testifies to the fact that processes underlying the onset of menopause, as well as the drop in production of estrogens occurring in this period, do not influence the formation of 17-oxycorticosteroids in the organism.

These data are in complete agreement with our observations on the influence of treatment of patients with climacteric neurosis with estrogens on the level of 17-oxycorticosteroids in the plasma. Administering, for two to four weeks, moderate and small doses of estradiol dipropionate (0.1 to 0.5 mg two to three times a week), ethinyl estradiol (0.005 to 0.01 mg per day), and folliculin (2500 to 5000 international units two to three times a week), we did not notice in 35 patients any regular deviations in the level of the free 17-oxycorticosteroids in the plasma, the values remaining at all times within the limits of normal variation.

In the studies of Tiliaferro and associates (17), Wallace and associates (18), and Robertson and associates (19), who administered to men with prostatic cancer large doses of estrogens, it was noted that there was a significant increase in the 17-oxycorticosteroids of the blood.

In the experimental studies of Zondek (20), which indicated an increase in the excretion and production of corticosterone upon administration of estrogens, and in the studies of Vogt (21), which gave evidence of a reduction in excretion, large doses of estrogens were likewise used which considerably exceeded the limits of physiologic variation of

production of them in the organism.

The reaction of the adrenal cortex to estrogens under these conditions cannot reflect their reaction to physiologic variations in the production of estrogens. Large doses of estrogens used in these studies may have acted as stressors, with resultant influence on the increased production of 17-oxycorticosteroids in the adrenals. Finally, the experimental conditions in several of the studies (21) were far from physiological. All of this explains the divergence of our findings obtained in women with physiologic hypoestrogenemia receiving moderate and small doses of estrogens from the findings in the literature, which were obtained with the use of large doses of estrogens.

The absence of differences in the content in the blood and urine of 17-oxycorticosteroids in women 40-54 years, with menopause and with and without menopausal neurosis, indicates that age changes of a pathologic nature in the higher vegetative nervous centers (hypothalamic centers), corresponding to the characteristic vegetative nervous disturbances in menopausal neurosis, also do not influence the content of 17-oxycorticosteroids in the blood and urine and, most likely, do not influence their formation in the adrenals.

These data, which indicate a progressive decrease in the urinary excretion of neutral 17-ketosteroids in women with increasing age, are in complete agreement with the findings in the literature. However, our studies of the excretion of 17-ketosteroids in women with menopause of varying duration indicated an absence in them of changes of this excretion as compared with the same age group with continued menstrual cycles, and are at variance with the findings of Hamblen and others (9, 10), who observed an increased excretion of 17-ketosteroids following the onset of menopause. It should be noted that the conclusions of Hamblen are based on a study of very few women of different ages and were not processed statistically, which diminishes their reliability. The necessity of taking a critical attitude toward Hamblen's conclusions is further evident in his failure to detect any difference in the urinary excretion of 17-ketosteroids in women in the 62-74 year group from those in the 21-43 year group, which is in disagreement with the few data in the literature, all of which indicate a drop in excretion with aging and in old age.

In examining the material presented by Santo-Ruiz, Wurterle (8) also did not confirm the increased excretion of 17-ketosteroid compounds during the climacteric.

The presence of menopausal neurosis, according to our findings, also did not influence the urinary excretion of 17-ketosteroids.

Hence, neither in the process of aging withing the age groups which we studied (30-39, 40-49, and 50-59 years), nor in the different periods of menopause (less than two, and from two to five years after onset), nor in the presence of menopausal neurosis, were we able to observe any changes in the content in the blood (with the exception of the 50-59 year group) or in the urinary excretion of 17-oxycorticosteroids, and consequently we were unable to demonstrate changes in the production of these compounds. We also failed to show an influence of moderate doses of estrogens on this function of the adrenal cortices.

With respect to the urinary excretion of 17-ketosteroids in the process of aging, we detected a decline in their excretion, which is in accord with numerous data of the literature. At the same time, we could not, during the different periods of the menopause or in the presence of climacteric neurosis, demonstrate changes in excretion of them, exceeding the limits of normal age changes. All of this gives evidence that, in the process of aging there are no substantial changes in the adrenal production of 17-oxycorticosteroids despite the presence of disturbances in the formation of C₁₉-steroids. Processes leading up to menopause and the climacteric neurosis, physiologic changes developing during definite periods of the menopause in the level of production of estrogens, and the use of moderate and small doses of estrogens, do not influence either the content in the blood or the urinary excretion of 17-oxycorticosteroids or the excretion of 17-ketosteroids.

The absence in women, during the process of aging and in the climacteric, of a drop in the production of 17-oxycorticosteroids in the presence of a diminished production of C₁₉-steroids may be a factor of considerable significance in pathologic physiology.

The maintenance of a high level of adrenal cortical function with respect to the production of 17-oxycorticosteroids is of undoubted importance in the adaptation of the organism during the period of aging to physiologic and pathologic stimuli. Corresponding to this is the retention, in aging, of the reaction of the adrenals to ACTH at levels characteristic of the reproductive age (22). It is necessary to keep this in mind in the different areas of medicine. The importance of the adrenal cortex in the process of adaptation, as shown by Selye and confirmed by a number of other investigators, can scarcely be disputed at the present time.

The detectable divergence in the dynamics of formation of certain hormones in the process of aging - the maintenance of a high level of production of 17-oxycorticosteroids in

the presence of a reduced production of estrogens and androgens - is unquestionably of great physiologic significance. But under certain conditions, disturbances in relationships in the formation of these hormones are conceivably a factor which is of importance in the pathogenesis of certain diseases.

Albright (23) expressed the opinion that, in the pathogenesis of osteoporosis in aging individuals, great importance attaches to a decline in the production of hormones with anabolic protein effects (androgens and estrogens) despite a continued high production of corticosteroids, with its attendant catabolic protein effect. This explains the favorable therapeutic effect achieved with the use of estrogens and androgens in osteoporosis in elderly persons.

Our own data, which indicate the presence in women during aging of a content in the blood and urinary excretion of 17-oxycorticosteroids at the level observed during the reproductive years, along with a progressive fall in 17-ketosteroids, and the findings obtained in our laboratory by O. N. Savchenko concerning the marked drop in the urinary excretion of estrogens during the two to five years after the onset of menopause, are in complete concordance with Albright's position.

Changes in the relationship, during aging processes in women, of the production of 17-oxycorticosteroids and estrogens may also be of importance in the age changes in the metabolism of lipids and of lipoproteins. It is known that the use of 17-oxycorticosteroids causes an increase in the level of serum cholesterol (24) along with a drop in the phospholipid/cholesterol coefficient (25) and an increase in beta- and O-lipoproteins (26), whereas the use of estrogens leads to a decline in the cholesterol level with a decrease in the phospholipid/cholesterol coefficient and in the percentage of beta-lipoproteins (27, 28, 29, 30).

The studies of Ya. V. Blagosklonnaya (31), carried out in our laboratory, have shown that a decline in the level of hypercholesterolemia could almost regularly be achieved even with the use of moderate doses of estrogens, and this result is perpetuated with the subsequent use of small maintenance doses. Rafal'skiy, pursuing these studies further in our laboratory, has shown that, in a number of patients, small doses of estrogens - at the limit of their effect in causing proliferation of the vaginal mucosa - also reverse hypercholesterolemia with continued use, reduce the cholesterol/phospholipid coefficient, and decrease the percentage of beta-lipoproteins. These findings show that even small changes in the level of estrogens in the organism may lead to changes in the metabolism of lipids and of lipoproteins.

Possibly, the continued production of 17-oxycorticosteroids by the adrenal cortex (and its increase in the 50-59 year group) in the presence of decreased production of estrogens by the ovaries, is particularly important in certain periods of the menopause (especially after two years following onset of the menopause), and is a factor resulting in the marked increase in the blood cholesterol, in the cholesterol/phospholipid coefficient, and in the percentage of beta-lipoproteins in women during the course of aging.

But whereas the problem of the role of estrogens in the pathogenesis of atherosclerosis has been decided in the affirmative by numerous clinical and experimental proofs, the problem of the role of 17-oxycorticosteroids in the pathogenesis of this disease remains highly complicated. As shown by studies of Wang and associates (25) and by Adlersberg (32), cortisone and hydrocortisone increase the blood cholesterol level and, at the same time, impede the development of experimental atherosclerosis.

The data of Wang and other authors have been confirmed by Stamler and associates (33), who did not observe in roosters, following injections of hydrocortisone, any increase in the atherogenesis of the aorta and of the coronary arteries while being fed cholesterol, despite the development of marked cholesterolemia. However, White (34) reported an increase in mice of lipid deposition, under the influence of these steroids, in the walls of the larger blood vessels.

Thus, the data concerning the influence of 17-oxycorticosteroids on the metabolism of lipids and of lipoproteins, the problem of the role of these corticosteroids in the pathogenesis of atherosclerosis still remains unresolved: should we consider the absence of an age reduction in the level of 17-oxycorticosteroids in the plasma of women in the 40-49 year group and the slight increase in the 50-59 year group as a factor facilitating or, on the contrary, inhibiting the development of this disease? However, it may be regarded as established that 17-oxycorticosteroids are an active factor in the metabolism of lipids and of lipoproteins, with which the pathogenesis of atherosclerosis is associated.

The absence of a reduced level of 17-oxycorticosteroids in the blood and urine during the period of aging makes it essential also to clarify their role in the genesis of certain other diseases occurring in this age period (such as hypertension, diabetes mellitus, etc.).

Examining the question of the production of 17-oxycorticosteroids and of C₁₉-steroids in the process of aging and of their role in the formation of certain physiologic and pathologic conditions, it is necessary to take into account

the role of the hypothalamic centers (neurosecretions) and of the anterior lobe of the pituitary in the regulation of this production. One should not dis sever these processes from the regulating influence of other organs and systems of organs, especially the cerebral cortex, also. The role of the adrenal cortex in the genesis of different physiologic and pathologic states (including stress) may be examined only within the system of this entire regulatory complex.

Conclusions

(1) In women aged 39-39, 40-49, and 50-59 years, we have noticed an increase in the average content of free 17-oxycorticosteroids in the plasma in the 50-59 year group, in the absence of differences in their content in other age groups, and an absence of differences in the urinary excretion of total and free 17-oxycorticosteroids. The daily excretion of 17-ketosteroids in the urine diminishes progressively with increasing age.

(2) In women at different periods of the menopause (less than two years, and from two to five years after onset), and in women of the same age but with continued menses, there is no difference in the content of free 17-oxycorticosteroids in the plasma or in the urinary excretion of 17-oxycorticosteroids and 17-ketosteroids.

(3) In women of the 40-54 year group with menopause, there is no difference in the average level of 17-oxycorticosteroids of the plasma in groups with menopausal neurosis and in those without it.

(4) The data obtained indicate that, in the process of aging and in old age, there are disturbances in women in the formation of C_{19} -steroids in the absence of any evidence of disturbances in the formation of 17-oxycorticosteroids.

(5) The processes underlying menopause and climacteric neurosis, and physiologic hypoestrogenemia, do not influence the formation of C_{19} -steroids or of 17-oxycorticosteroids.

(6) The absence of a reduction in the formation of 17-oxycorticosteroids during the process of aging may be important in ensuring the necessary level of certain physiologic reactions (for example, stress) and in the pathogenesis of certain pathologic conditions - osteoporosis, disturbances in the metabolism of lipids and lipoproteins, as well as certain other affections developing with increasing age.

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